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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,275	03/01/2005	John S. Wai	21162YP	8334

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EXAMINER	
MURRAY, JEFFREY H	
ART UNIT	**PAPER NUMBER**
1624	
MAIL DATE	**DELIVERY MODE**
02/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,275	WAI ET AL.	
	Examiner	Art Unit	
	JEFFREY H. MURRAY	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18 and 20* is/are pending in the application.

4a) Of the above claim(s) *18 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/1/2005 & 11/2/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. This action is in response to a restriction election filed on January 14, 2008. There are eighteen claims pending and sixteen under consideration. Claims 17 and 19 were cancelled. Claims 18 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 14, 2008. The applicants have elected Group IV with traverse. This is the first action on the merits. This present invention is directed to dihydroxypyridopyrazine-1,6-diones and pharmaceutically acceptable salts thereof, their synthesis, and their use as inhibitors of the HIV integrase enzyme. The compounds of the present invention and their pharmaceutically acceptable salts are useful for preventing or treating infection by HIV and for treating, delaying the onset of, or preventing AIDS.

2. Applicant's election with traverse of Group IV in the reply filed on January 14, 2008 is acknowledged. The traversal is on the ground(s) that there is a technical relationship between the separately grouped claims. This is found persuasive in part. The examiner agrees with the applicants in that Groups V-VIII are merely a subset of Groups I-IV. Applicants have chosen Group IV which will encompass compounds and compositions of the former Group VIII. Therefore, these four subsets (V-VIII) will be examined with the elected group.

Examiner does not, however, find persuasive the argument that there would be no serious burden on the examiner in conducting a search on Groups I-IV and IX-XX. As noted prior, these compounds can possess a third fused ring which may be a cyclopropyl, phenyl, or pyridyl ring. These various tricyclic ring systems can cause different search burdens to arise. For example, a bicyclic ring core such as 8,9-dihydroxy-3,4-dihydro-1H-pyrido[1,2-a]pyrazine-1,6(2H)-dione is different from a tricyclic ring core such as 7,8-dihydroxy-5H-dipyrido[1,2-a:4',3'-e]pyrazine-6,10-dione. Thus, separate searches in the literature would be required. Each group's compounds are made and used independently of each other and could support separate patents. One skilled in the art would not consider such diverse structures as functional equivalents of each other. The mere fact that there is a single similarity is not in itself a significant reason to render the whole embodiment obvious. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Priority

3. Acknowledgment is made of Applicant's claim for domestic priority. This application, U.S. Application No. 10/526,275, filed on March 1, 2005, is a national stage application of PCT/US03/28366, filed on September 10, 2003, claims domestic priority to U.S. Provisional Application No. 60/409,741, filed September 11, 2002.

Specification

4. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

Claim Rejections - 35 USC § 112, 1st paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of Formula (I) where R^1 is an optionally substituted benzyl group and R^2, R^3 and R^4 are either hydrogen or an optionally substituted alkyl group, the specification does not reasonably provide enablement for any other compounds or compositions not previously defined by the R variables. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the compounds and compositions of the invention commensurate in scope with these claims.

7. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (*United States v. Teletronics* Inc., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte*

Forman 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) *Amount of guidance provided by Applicant.* Applicant has provided no guidance, examples, or provided any chemical or biological data and/or testing results of any compounds of Formula (I) where R^1 is other than an optionally substituted benzyl group and R^2, R^3 and R^4 are hydrogen or an optionally substituted alkyl group. Applicant has only shown a select number of compounds or compositions within the specification and of these, none of them fall outside of the scope of enablement mentioned here.

2) Unpredictability in the art. Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of

> structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) ..... " Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

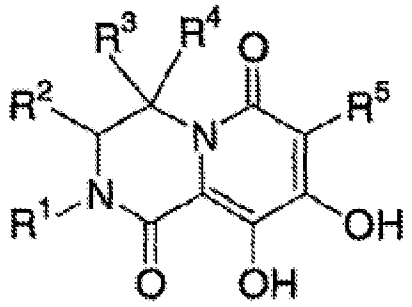
The scope of any compounds where the R variables are not those previously described above is not adequately enabled or defined. Applicants have provided no guidance as how the compounds are made more active *in vivo*.

3) *Number of working examples*. Applicant has provided no working examples of any compounds or compositions where the R variables are other than those described above. There is not seen any guidance or direction to consider disclosures in the art to prepare the diverse compounds and compositions instantly claimed. Applicants bear the responsibility to teach how to make the compounds set forth in their claims.

4) *Nature of the invention*. The nature of this invention relates to dihydroxy-pyridopyrazine-1,6-diones and pharmaceutically acceptable salts thereof, their synthesis, and their use as inhibitors of the HIV integrase enzyme. The compounds of

the present invention and their pharmaceutically acceptable salts are useful for preventing or treating infection by HIV and for treating, delaying the onset of, or preventing AIDS.

5) Scope of the Claims. The scope of the claims is all of the tens of thousands of compounds represented by general formula (I):



thus the scope of the claims is very broad.

6) *Level of skill in the art*. The artisan using Applicants invention would be a chemist with a M.S. or Ph.D. degree, and having several years of bench experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is not enabled for making these compounds or compositions.

Claim Rejections - 35 USC § 112, 2nd paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 15 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 15 is rejected because the claim states, "and pharmaceutically acceptable salts thereof." whereby the claim is improper in its number. Claims must be directed to a ***single invention***, not a plurality of inventions. Examiner suggests to applicant to change the claims to read, "…" or a pharmaceutically acceptable salt thereof." No new matter permitted. Appropriate correction is required.

11. Claim 16 recites the limitation: "…a therapeutically effective amount of…" The claim does not define what it is a "therapeutically effective amount" for. Without describing what purpose the compound or composition is being used for, it is impossible to determine what is a "therapeutically effective amount." Examiner suggests removing the words, "a therapeutically effective amount of" from this claim. Appropriate correction is required.

Conclusion

12. Claims 1-16 are rejected.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is (571) 272-9023. The examiner can normally be reached on Mon-Thurs. 7:30-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a US PTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey H Murray/
Patent Examiner
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